

REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 21, 25-29, 33, 36, 37, 39-45, 47-53 and 56 are pending in the application, with claims 21, 45 and 56 being in independent format.

Claim 21 has been amended to recite a method for treating migraine headaches and symptoms of migraine headaches consisting essentially of administering a $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonist. Support for this amendment may be found, for example, in previously presented claim 54 and throughout the specification as originally filed. Claim 35 has been cancelled from the application. Claims 36 and 37 have been amended to replace reference to claim 35 with reference to claim 21. Claim 38 has been cancelled from the application, and claims 39, 40, 42, 44, 47-51 and 53 have been amended to replace reference to cancelled claim 38 with reference to newly added claim 56. Claim 45 has been amended to include the language of claim 46, namely that the cation chloride cotransporter antagonist is selected from the group consisting of: thiazide; and thiazide-like compositions. Newly added claim 56 is drawn to methods for treating migraine headaches and symptoms of migraine headaches comprising administering a treatment composition comprising a $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonist selected from the group consisting of bumetanide and ethacrynic acid. Support for newly added claim 56 may be found, for example, in previous claim 27, and throughout the specification as originally filed.

It is urged that there is a clear basis in the specification as filed, for all the above amendments and that none of the amendments constitute new matter.

Claim Rejections – 35 USC §112, first paragraph

Claim 45 stands rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure. Specifically, the Examiner has stated that the specification does not provide enablement for the use of a “cation chloride cotransporter antagonist” to treat migraine.

While applicant does not acquiesce in this rejection, claim 45 has been amended to clarify that the cation chloride cotransporter antagonist is a thiazide or a thiazide-like composition.

It is urged that, following this amendment, all the pending claims satisfy the requirements of 35 USC §112, first paragraph, and that this rejection may therefore be properly withdrawn.

Claim Rejections – 35 USC §102

Claims 21, 27, 28, 35-38, 45 and 46 stand rejected under 35 USC §102(b) as being anticipated by Mathew et al. (*Neurology* 46:1226-1230, 1996). This rejection is respectfully traversed.

As noted in the Amendment and Reply filed on November 24, 2004, Mathew et al. studied patients with refractory transformed migraine type of chronic daily headache (CDH), and showed that a *subset* of these patients who were treated after diagnosis of increased intracranial pressure with a combination of antimigraine agents, acetazolamide *and* furosemide showed reduced number of days of severe headache and overall improvement in quality of life. Mathew et al. clearly state that the furosemide was administered to reduce increased intracranial pressure.

Mathew et al. do not teach a method for the treatment of migraine consisting essentially of administering an effective amount of a $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonist as recited in amended claim 21, nor do they teach methods for treating migraine by administering a cation chloride cotransporter antagonist selected from the consisting of thiazide and thiazide-like compositions as recited in amended claim 45, or a $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonist selected from the group consisting of bumetanide and ethacrynic acid as recited in newly added claim 56.

Applicant thus submits that Mathew et al. do not teach or suggest the presently claimed methods and that the rejection of the claims under 35 USC §102(b) may be properly withdrawn.

Claim Rejections – 35 USC §103

Claims 25, 26, 29, 33, 39-44 and 47-53 stand rejected under 35 USC §103(a) as being unpatentable over Mathew et al. in view of Levin (US Patent 66,432,986), Bentley et al. (US Patent 6,369,094) and Becker et al. (US Patent 5,256,687). This rejection is respectfully traversed.

The teachings of Mathew et al. are discussed above. The Examiner states that Levin and Bentley et al. demonstrate the routine knowledge in the art of various methods of delivery, formulations and dosage forms for anti-migraine agents, and further that Becker et al.

demonstrates the routine knowledge in the art of using mannitol as a carrier for furosemide. However none of these references overcome the deficiencies of Mathew et al. discussed above.

It is submitted that neither Mathew et al., Levin, Bentley et al. nor Becker et al., taken either singly or in combination, teach or suggest the presently claimed methods and that this rejection of claims 25, 26, 29, 33, 39-44 and 47-53 under 35 USC §103(a) may thus be properly withdrawn.

Claims 25, 26, 33, 39, 40 and 53-55 stand rejected under 35 USC §103(a) as being unpatentable over Mathew et al. in view of Read et al. (Cephalalgia, December 1997, 17:826-832). Specifically, the Examiner asserts that the teachings of Mathew et al. and Read et al. would have rendered obvious the use of furosemide alone to treat migraine. This rejection is respectfully traversed.

As discussed in the Amendment and Reply filed on November 24, 2004, applicant's research indicates that the December 1997 issue of Cephalalgia was not received by any subscriber on or before the December 23, 1997 priority date of the present application, and that the Read et al. reference is therefore not prior art to the present application. Even if further investigation were to show that selected subscribers *did* receive the December 1997 issue of Cephalalgia prior to the December 23, 1997 priority date, it is submitted that combining the teachings of Mathew et al. and Read et al. would not have rendered applicant's claimed methods obvious to one of skill in the art at the time the application was filed.

As discussed previously, Mathew et al. describe studies in which administration of a combination of both furosemide and acetazolamide together with known anti-migraine agents lead to improved control of symptoms in a subset of patients with refractory transformed migraine type of chronic daily headache (CDH) who had also been identified as having increased intracranial pressure (also referred to as idiopathic intracranial hypertension; IIH). Mathew et al. conclude that their observations indicate a possible link between migraine and IIH. Mathew et al. do not teach or suggest that administration of furosemide and/or acetazolamide in the absence of conventional anti-migraine agents would be effective in relieving the symptoms of migraine.

Read et al. present experimental data showing that furosemide inhibits regenerative cortical spreading depression in anaesthetized cats, and speculate that compounds with the ability to modify cortical spreading depression *may* have potential as anti-migraine compounds.

While one of skill in the art, at the time the application was filed, *might* have been motivated to combine the teachings of Mathew et al. with those of Read et al., applicant submits that the combined teachings would not have led one of skill in the art to reasonably believe that furosemide alone could be *successfully* employed in the treatment of migraine. It was not until applicant's elucidation of the role of $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonists in modulating (reducing) the synchronization of neuronal population activity that is associated with seizure disorders and migraine headaches, that one of ordinary skill in the art would have had any reasonable expectation that $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransporter antagonists, such as furosemide, would be effective in treating migraine headaches and symptoms.

It is urged that neither the teachings of Mathew et al. nor those of Read et al., taken either singly or in combination, would have rendered the presently claimed methods obvious to one of skill in the art at the time the application was filed, and that the rejection of claims 25, 26, 33, 39, 40 and 53-55 under 35 USC §103(a) may thus be properly withdrawn.

Conclusion

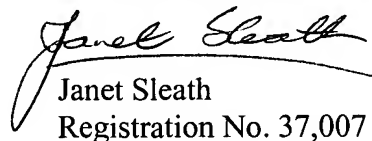
Early reconsideration and allowance of the pending claims is respectfully requested. If the Examiner has any further concerns regarding the application, he is invited to telephone the undersigned at 206.382.1191.

A Request for a One Month extension of Time, extending the deadline for response to the Office Action to November 13, 2005, is submitted herewith.

Charge Deposit Account

Please charge any additional fees that may be required, or credit any overpayment, to our Deposit Account No. 19-3555.

Respectfully submitted,


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